

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-36. (Cancelled)

37. (Withdrawn) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

- a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment, and
- b) a solid matrix composed of an extruded and injection molded pharmaceutical composition comprising
 - i) a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molecular weight of about 220,00 and a ratio of free carboxyl groups to ester groups of 1:10 present in an amount of about 15 to 50% w/w;
 - ii) at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 20 % to about 70 % w/w,
 - iii) a lubricant present in an amount of about 10% to about 25% w/w;
 - iv) at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, a wicking agent, or an inorganic salt, in combination or mixture thereof, present in an amount of about 2.5 % to about 70% w/w;
 - v) a surfactant present in an amount of 0 to 10%,
 - vi) a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w, and optionally containing a drug substance,

the polymer composition producing an erodible, and a pH-independent formulation in a patient's gastro-intestinal environment, and in which, at least prior to administration to a patient, the sub-units of a) and b) are assembled into a dosage form.

38. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37, in which the two hydroxypropylcellulose polymers of differing molecular

weight, has as a first polymer a viscosity in the range of 200-600 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000, and the second polymer has a viscosity of 150-400 mPas at 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 140,000, each present in an amount of about 30 to 32% w/w.

39. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37, in which the two hydroxypropylcellulose polymers of differing molecular weight, has as a first polymer a viscosity of 150-400 mPas at 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 140,000, and the second polymer has a viscosity in the range of 150-400 mPas at a 2% concentration in aqueous solution at 25 °C, and a molecular weight of about 370,000 each present in an amount of about 30 to 32% w/w.

40. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37, in which the two hydroxypropylcellulose polymers of differing molecular weight, has as a first polymer a viscosity in the range of 200-600 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000 and the second polymer has a viscosity in the range of 150-400 mPas at a 2% concentration in aqueous solution at 25 °C, and a molecular weight of about 370,000, each present in an amount of about 30 to 32% w/w.

41. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37, in which the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or a combination or mixture thereof.

42-43. (Cancelled)

44. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 41 wherein the lubricant is stearyl alcohol.

45. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 41 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

46. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycolate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone; a swellable solid selected from polyvinylpyrrolidone, ethyl cellulose, cellulose acetate phthalate, a third hydroxypropyl cellulose polymer, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate; a non-reducing sugar selected from xylitol, or mannitol; a water soluble filler selected from lactose, or starch; an inorganic salt which is sodium chloride; or a combination or mixture thereof.

47. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 46 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycolate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination or mixture thereof.

48. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 47 wherein the disintegrant is present in the range of about 10 to 40% w/w.

49. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 48 wherein the disintegrant is present in the range of about 20 to about 30% w/w.

50. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 46 wherein the at least one dissolution modifying excipient is a swellable solid selected from polyvinyl pyrrolidone copovidone; ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate, or a combination or mixture thereof.

51. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 46 wherein the at least one dissolution modifying excipient includes a second dissolution modifying excipient which is a wicking agent.

52. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 51 wherein the wicking agent is lactose.

53. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, castor oil; or a combination or mixture thereof.

54. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the processing agent is talc present in an amount of about 1 to about 5 % w/w.

55. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the solid matrix composition further comprises an absorption enhancer.

56. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 55 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; or a combination or mixture thereof.

57. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the copolymer is present in an amount of about 15 to about 30% w/w.

58. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the surfactant is present in an amount of less than 5% w/w.

59. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 58 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

60. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 57 wherein the sodium dodecyl sulphate is present in an amount of less than 2% w/w.

61. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the composition comprises a lubricant which is stearyl alcohol, a surfactant, the at least one dissolution modifying excipient is a swellable solid, and the compositions further comprises a second dissolution modifying excipient which is sodium starch glycollate and/or croscarmellose sodium.

62. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 61 wherein the surfactant is SDS, present at 2% w/w or less, and the swellable solid are present at less than <20% w/w.

63. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 61 wherein the sodium starch glycollate and/or croscarmellose sodium are present in about 10% w/w.

64. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the copolymer is present in an amount of about 15 to 25% w/w, the lubricant is stearyl alcohol, the at least one dissolution modifying excipient is sodium starch glycolate, the surfactant is sodium dodecyl sulfate or a block copolymer of ethylene oxide and propylene oxide.

65. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two HPC polymers have a resulting molecular weight of about 30,000 to about 370,000.

66. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two HPC polymers have a resulting molecular weight of about 50,000 to about 170,000.

67. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two HPC polymers have a resulting molecular weight of about 80,000 to about 140,000.

68. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two hydroxypropyl cellulose polymers are independently selected from the group consisting of

a polymer having a viscosity in the range of 150-700 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000;

a polymer having a viscosity in the range of 200-600 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000;

a polymer having a viscosity in the range of 300-600 mPas at a 10% concentration in aqueous solution at 25 °C and a molecular weight of about 80,000;

a polymer having a viscosity of 150-400 mPas at 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 140,000; ;

a polymer having a viscosity in the range of 75 –150 mPas at a 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 95,000;

a polymer having a viscosity in the range of 150–400 mPas at a 2% concentration in aqueous solution at 25 °C, and a molecular weight of about 370,000;

a polymer having a viscosity of 6.0-10.0 mPas at a 2% concentration in aqueous solution at 20 °C; and

a polymer having a viscosity of 150-400 mPas at a 2% concentration in aqueous solution at 20 °C.

69. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two hydroxypropyl cellulose polymers are present in equal w/w % amounts of each component.

70. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the at least two hydroxypropyl cellulose polymers are present in an amount of about 32% w/w of each polymer.

71. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the solid matrix is composed of a pharmaceutical composition comprising:

Component	%w/w				
	A	or	B	or	C
Eudragit 4135F	24.0		24.0		24.0
Stearyl alcohol	12.0		12.0		12.0
Klucel EF	30.0		30.0		0.0
Klucel JF	30.0		0.0		30.0
Klucel GF	0.0		30.0		30.0
sodium starch glycolate	2.0		2.0		2.0
sodium dodecyl sulfate	1.0		1.0		1.0
polyoxypropylene-polyoxyethylene block copolymers	1.0		1.0		1.0
Total	100		100		100

72. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 37 wherein the solid matrix is composed of a pharmaceutical composition comprising:

Component	% w/w				
	A	or	B	or	C
Eudragit 4135F	24.0		29.0		21.0
Stearyl alcohol	12.0		12.0		12.0
Klucel EF	32.0		25.0		32.0
Klucel JF	32.0		30.0		32.0
sodium starch glycolate	0.0		2.0		2.0
sodium dodecyl sulfate	0.0		1.0		0.0
polyoxypropylene-polyoxyethylene block copolymers	0.0		1.0		1.0
Total	100		100		100

73. (Currently amended) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being extruded and injection moulded and each sub-unit being selected from

a) a drug substance-containing capsule compartment providing pulsatile release of a drug, comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, wherein the shell is composed of a shell material and wherein the shell is composed of an extruded and injection molded pharmaceutical composition comprising

i) a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molecular weight of about 220,000 and a ratio of free carboxyl groups to ester groups of 1:10 present in an amount of about 15 to about 50 % w/w,

ii) at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 20 % to about 70 % w/w, wherein either one hydroxypropylcellulose polymer is one with an average molecular weight of 80,000 and having a solution viscosity of 300-600 mPas when dissolved in 10 weight % in water at 25°C, and a second hydroxypropylcellulose polymer is one with an average molecular weight of 140,000 and having a solution viscosity of 150-400 mPas in 5 weight % in water at 25°C of, or one hydroxypropylcellulose polymer is one with an average molecular weight of 80,000 and having a solution viscosity of 300-600 mPas in 10 weight % in water at 25°C and a second hydroxypropylcellulose polymer is one with an average molecular weight of 370,000 and having a solution viscosity of 150-400 mPas in 2 weight % in water at 25°C;

iii) a lubricant present in an amount of about 10% to about 25% w/w;

iv) at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, a wicking agent, or an inorganic salt, in combination or mixture thereof, present in an amount of about 2.5% to about 70% w/w;

v) a surfactant present in an amount of 0 to 10%, and

vi) a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w; and

wherein the pharmaceutical composition produces an erodible, and a pH-independent formulation in the patients gastro-intestinal environment for release of the drug

substance contained in the capsule compartment, and wherein the shell material between and including the inner and outer surfaces is comprised of the extruded and injection material; and

b) a solid sub-unit comprised of a pharmaceutical polymer composition, having an outer surface, the outer surface being exposed to a gastro-intestinal environment, optionally containing a drug substance, the pharmaceutical polymer composition being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment for release of the a drug substance contained in the a solid matrix, and in which, at least prior to administration to a patient, the sub-units of a) and b) are assembled into a dosage form.

74. (Previously Presented) The multicomponent pharmaceutical dosage form according to Claim 73, in which at least one of the sub-units is a drug substance-containing capsule compartment having a wall with a thickness in the range of about 0.3 – 0.8 mm.

75. (Previously Presented) The multicomponent pharmaceutical dosage form according to Claim 73, in which the drug substance-containing capsule compartment of a) and the solid sub-unit of b) differ in their dissolution or disintegration characteristics in the patient's gastro-intestinal environment.

76. (Cancelled)

77. (Currently amended) The multi-component pharmaceutical dosage form according to Claim ~~37~~ 73, in which the drug substance-containing capsule compartment comprises as two hydroxypropylcellulose polymers of differing molecular weights, the first polymer having a viscosity in the range of ~~200~~ 300-600 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000, and the second polymer having polymer having a viscosity of 150-400 mPas at 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 140,000, each present in an amount of about 30 to 32% w/w.

78. (Cancelled)

79. (Currently amended) The multi-component pharmaceutical dosage form according to Claim ~~37~~ 73, in which the drug substance-containing capsule compartment comprises as two hydroxypropylcellulose polymers of differing molecular weights, the first polymer having a viscosity in the range of ~~200~~ 300-600 mPas at a 10% concentration in aqueous solution at 25 °C, and a molecular weight of about 80,000 and the second polymer having a viscosity in the range of 150-400 mPas at a 2% concentration in aqueous solution at 25 °C, and a molecular weight of about 370,000, each present in an amount of about 30 to 32% w/w.

80. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73, in which the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or a combination or mixture thereof.

81. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 80 wherein the lubricant is stearyl alcohol.

82. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 81 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

83. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone; a swellable solid selected from polyvinylpyrrolidone, ethyl cellulose, cellulose acetate phthalate, a third hydroxypropyl cellulose polymer, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate; a non-reducing sugar selected from xylitol, or mannitol; a water soluble filler selected from lactose, or starch; an inorganic salt which is sodium chloride; or a combination or mixture thereof.

84. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 82 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium,

crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination or mixture thereof.

85. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 84 wherein the disintegrant is present in the range of about 10 to 40% w/w.

86. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 81 wherein the disintegrant is present in the range of about 20 to about 30% w/w.

87. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 73 wherein the at least one dissolution modifying excipient is a swellable solid selected from polyvinyl pyrrolidone copovidone; ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate, or a combination or mixture thereof.

88. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 87 wherein the at least one dissolution modifying excipient includes a second dissolution modifying excipient which is a wicking agent.

89. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 90 wherein the wicking agent is lactose.

90. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, castor oil; or a combination or mixture thereof.

91. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the processing agent is talc present in an amount of about 1 to about 5 % w/w.

92. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the solid matrix composition further comprises an absorption enhancer.

93. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 92 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; or a combination or mixture thereof.

94. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the copolymer is present in an amount of about 15 to about 30% w/w.

95. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the surfactant is present in an amount of less than 5% w/w.

96. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 95 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

97. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 96 wherein the sodium dodecyl sulphate is present in an amount of less than 2% w/w.

98. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the composition comprises a lubricant which is stearyl alcohol, a surfactant, the at least one dissolution modifying excipient is a swellable solid, and the compositions further comprises a second dissolution modifying excipient which is sodium starch glycolate and/or croscarmellose sodium.

99. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 98 wherein the surfactant is SDS, present at 2% w/w or less, and the swellable solid are present at less than <20% w/w.

100. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 98 wherein the sodium starch glycolate and/or croscarmellose sodium are present in about 10% w/w.

101. (Previously Presented) The multi-component pharmaceutical dosage form according to Claim 73 wherein the copolymer is present in an amount of about 15 to 25% w/w, the lubricant is stearyl alcohol, the at least one dissolution modifying excipient is sodium starch glycolate, the surfactant is sodium dodecyl sulfate or a block copolymer of ethylene oxide and propylene oxide.

102-106. (Cancelled)

107. (Currently amended) The multi-component pharmaceutical dosage form according to Claim 73 wherein ~~the~~ a solid matrix is composed of a pharmaceutical composition comprising:

Component	-----%w/w-----					
	A	or	B	or	C	

Eudragit 4135F a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molecular weight of about 220,000 and a ratio of free carboxyl groups to ester groups of 1:10 present in an amount of about 15 to about 50 % w/w

24.0	24.0	24.0
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Stearyl alcohol	2.0	12.0	12.0
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Klucel EF hydroxypropylcellulose polymer with an average molecular weight of 80,000 having a solution viscosity of 300-600 mPas when dissolved in 10 weight % in water at 25°C

30.0	30.0	0.0
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Klucel JF	30.0	0.0	30.0
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Klucel-GF hydroxypropylcellulose polymer with an average molecular weight of 370,000 having a solution viscosity of 150-400 mPas in 2 weight % in water at 25°C

	0.0	30.0	30.0
sodium starch glycollate			
	2.0	2.0	2.0
sodium dodecyl sulfate			
	1.0	1.0	1.0
polyoxypropylene-polyoxyethylene block copolymers			
	1.0	1.0	1.0
Total	100	100	100

108. (Currently amended) The multi-component pharmaceutical dosage form according to Claim 73 wherein the solid matrix is composed of a pharmaceutical composition comprising:

Component -----% w/w-----
A or B or C

Eudragit 4135F a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molecular weight of about 220,000 and a ratio of free carboxyl groups to ester groups of 1:10 present in an amount of about 15 to about 50 % w/w

	24.0	29.0	21.0
Stearyl alcohol	12.0	12.0	12.0

Klucel-EF hydroxypropylcellulose polymer with an average molecular weight of 80,000 having a solution viscosity of 300-600 mPas when dissolved in 10 weight % in water at 25°C

	32.0	25.0	32.0
<u>Klucel-JF hydroxypropylcellulose polymer with an average molecular weight of 140,000 having a solution viscosity of 150-400 mPas in 5 weight % in water at 25°C</u>			

	32.0	30.0	32.0
sodium starch glycollate			
	0.0	2.0	2.0
sodium dodecyl sulfate			
	0.0	1.0	0.0
polyoxypropylene-polyoxyethylene block copolymers			
	0.0	1.0	1.0
Total	100	100	100 .